INDUCTION OF COLLATERAL SENSITIVITY BY AZA-PTEROCARPANS IN MULTIDRUG RESISTANT CHRONIC MYELOID LEUKEMIA CELLS

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Introduction and Objectives: The Multidrug Resistance (MDR) phenotype is a major challenge on cancer treatment. Therefore, development of drugs that act specifically on resistant cells, in a phenomenon known as Collateral Sensitivity (CS), is of great interest. Natural isoflavonoids are reported to present a variety of biological activities, being inspiration for the development of new antineoplastic agents. In our work, we studied the activity of two aza-pterocarpans, modified isoflavonoids, in MDR chronic myeloid leukemia cells.

Material and Methods: Three cell lines were used to comprehend the mechanism of action induced by the aza-pterocarpans: K562, parental and sensible to standard treatment; their MDR counterparts Lucena-1 and FEPS, selected respectively by exposure to vincristine or daunorubicin. Lucena-1 and FEPS were characterized by overexpression of ATP-binding cassette (ABC) proteins. Cells were incubated for 72 hours with different doses of each aza-pterocarp, WMA-233 or LQB-223, and their viability was measured by the MTT assay. To understand if these compounds could alter expression of the ABCB1 protein isoform, cells were incubated for 24 hours with WMA-233 or LQB-223 and protein expression was assessed by flow cytometry. In addition, ABCB1 activity was analyzed using Rhodamine-123.

Results and conclusion: While K562, Lucena-1 and FEPS were similarly susceptible to LQB-223, FEPS was more sensitive to WMA-233, suggesting collateral sensitization. However, this effect could not be associated to ABCB1 modulation, since flow cytometry showed no inhibition of its activity. LQB-223, however, was able to reduce ABCB1 expression in both MDR cell lines. FEPS differ from Lucena-1 since it also overexpresses two ABC isoforms, ABCB1 and ABCC1, suggesting that the latter could be a target for the CS-effect of WMA-233. Both compounds induced selective antitumoral activity, since there was no decrease in viability of PHA-activated peripheral blood mononuclear cells. Results suggest that these compounds are interesting precursors for new MDR-selective chemotherapeutic agents.

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